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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/464,414	12/16/99	THANAVALA Y	RPP:156CUS

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EXAMINER	
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ART UNIT	PAPER NUMBER
1651	17

DATE MAILED: 07/17/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/464,414	Thanavala
Examiner	**Art Unit**
Michele Flood	1651

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *May 2, 2001*

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-3, 7, 9, 10, 12, and 13* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideratio

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-3, 7, 9, 10, 12, and 13* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement

Application Papers

9) ☒ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

Continued Prosecution Application

The request filed on May 2, 2001 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/464,414 is acceptable and a CPA has been established. Acknowledgment is made of applicant's cancellation of Claims 4-6, 8, 11, and 14-19. An action on the CPA follows.

Claims 1-3, 7, 9-10, and 12-13 are under examination.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 7, 9-10 and 12-13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for providing a secondary boosting response in a mammal to a non-enteric pathogen antigen (NEPA), wherein the NEPA is hepatitis B surface antigen (HBsAg) comprising the instantly claimed process steps and instantly claimed ingredients, does not reasonably provide enablement for providing a secondary boosting response in a mammal to any and all NEPAs comprising the instantly claimed process steps and instantly claimed ingredients. The specification does not enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to a method for providing a secondary boosting immune response in a mammal to a specific antigen to a non-enteric pathogen (NEPA), the pathogen being a pathogen that invades through a breach in the skin and that does not raise a protective enteric immune response in mammals free of acquired immunity to the pathogen, said method comprising rendering the mammal immunoreceptive to the NEPA by prior immunization against a non-enteric pathogen containing the NEPA by vaccination by injection followed by oral administration by feeding the immunoreceptive mammal with transgenic potato containing the NEPA expressed in the potato to cause a secondary immune response to the oral administration specific to the NEPA stronger than a response specific to NEPA caused by the NEPA in the absence of the prior immunization by injection. The claims are further drawn to a method where the mammal is human. The claims are further drawn to a method, wherein the NEPA is an antigen specific to a non-enteric pathogen selected from the group consisting of those that cause hepatitis B, hepatitis C, hepatitis delta, yellow fever, dengue hemorrhagic fever, tetanus, yaws, relapsing fever, rat bite fever, bubonic plague and spotted fever. The claims are further drawn to a method wherein the human ingests sufficient plant material to provide from about 10 to about 100 micrograms of NEPA per kilogram of body weight of the human, wherein the human ingests sufficient plant material to provide from about 2 to about 5 grams of plant material per kilogram of body weight of the human, and wherein the human ingests said plant material a plurality of different times, said

times being separated from each other by at least 5 days, wherein the plurality of times is three times.

The specification broadly discloses non-enteric pathogens that invade the epidermis of mammals via punctures, abrasions, cuts or other breaches in the skin, e.g. blood transfusions which can be used as sources of NEPA to raise a protective enteric immune response in mammals. However, the specification does not provide sufficient guidance as to how one of ordinary skill in the art would provide an immune response in a mammal and/or a human to a NEPA other than the non-enteric pathogen antigen, hepatitis B surface antigen. The specification does not disclose other specific non-enteric pathogen antigens which have been subjected to the claim-designated therapeutic regimen, nor does the specification teach any methodology associated with the making of genetically altered plant materials expressing any other NEPA other than the non-enteric pathogen antigen, hepatitis B surface antigen. In regard to Claim 1, the specification other than the mere suggestion on page 1, lines 13-16 does not provide guidance as to how to use the instantly claimed invention to provide a secondary boosting response to any all diseases caused by a non-enteric pathogen that invade the epidermis of mammals via punctures, abrasions, cuts or other breaches in the skin. Moreover, there is inadequate guidance as to how one of ordinary skill in the art would use the instantly claimed invention to genetically altered potato plant material to express any and all non-enteric pathogens other than HBsAg.

Inventions targeted for human therapy bear a heavy responsibility to provide supporting evidence because of the unpredictability in biological responses to therapeutic treatment. The

standard of enablement is higher for such inventions because effective treatments for providing immunological responses to the instantly disclosed pathogens are relatively rare, and may be unbelievable in the absence of supporting evidence. Claims drawn to compositions intended for the administration of compounds to humans generally require supporting evidence which clearly define the ingredients or constituents contained therein because of the unpredictability in biological responses to therapeutic treatments. In order to enable the skilled artisan to practice the invention as claimed, applicant would have to demonstrate the functional effect and describe the effective amounts of each ingredient for the administration of the composition intended for a therapeutic treatment. Accordingly, it would take undue experimentation without a reasonable expectation of success to determine which amounts of the instantly claimed plant materials expressing a non-enteric pathogen selected from those pathogens which cause the diseases hepatitis C, hepatitis delta, yellow fever, dengue, hemorrhagic fever, tetanus, yaws, relapsing fever, rat bite fever, bubonic plague and spotted fever.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3, 7, 9-10, and 12-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1, line 2, is rendered vague and indefinite by the phrase "to a specific antigen to a non-enteric pathogen (NEPA) because it is unclear as to the meaning of the abbreviation. While the specification clearly defines the abbreviation "(NEPA)" as a "non-enteric pathogen antigen", on page 5, line 5, as drafted it appears that the term refers to a non-enteric pathogen. The lack of clarity makes the claims ambiguous and confusing.

Claim 1, line 3, is rendered vague and indefinite by the phrase "a protective enteric immune response" because it is uncertain as to the subject matter applicant intends to direct the invention. As drafted, it appears that the method is directed to a method of providing a secondary boosting immune response to a non-enteric pathogen antigen. However, reference to "a protective enteric immune response" confuses the subject matter of the invention. Does applicant intend to direct the subject matter to boosting "a protective enteric immune response" or to "a protective non-enteric immune response"? The metes and bounds of the claimed invention cannot be ascertained because the scope of the limitations are not clearly defined.

Claim 1, lines 5-6, is made vague and indefinite by the phrase "by prior immunization against a non-enteric pathogen containing the NEPA by vaccination by injection" because the phrase is very confusing. It is uncertain as to what is contained therein the injection. Does the injection comprise a non-enteric pathogen or NEPA, or both ?

Claim 1 is generally narrative and indefinite, failing to conform with current U.S. practice. The claim is so replete with grammatical and idiomatic errors that they are too numerous to be

listed separately; and, thus they are incomprehensible. The claim should be appropriately amended.

There is an apparent misspelling in Claim 3, line 3 and claim 16. Applicant may overcome the rejection by replacing the misspelled word "hemorrhagic" with the word hemorrhagic.

Applicant is advised that should claim 10 be found allowable, claim 12 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

All other claims depend directly or indirectly from rejected claims and are, therefore, also, rejected under U.S.C. 112, second paragraph for the reasons set forth above.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to

the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3, 7, 9-10, and 12-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Arntzen et al. (A, US Patent 5,914,123) or Arntzen et al. (B, US Patent 6,136,320) in view of Stites (U), and further in view of readily admitted prior art.

Applicant claims a method for providing a secondary boosting immune response in a mammal to a specific antigen to a non-enteric pathogen (NEPA), the pathogen being a pathogen that invades through a breach in the skin and that does not raise a protective enteric immune response in mammals free of acquired immunity to the pathogen, said method comprising rendering the mammal immunoreceptive to the NEPA by prior immunization against a non-enteric pathogen containing the NEPA by vaccination by injection followed by oral administration by feeding the immunoreceptive mammal with transgenic potato containing the NEPA expressed in the potato to cause a secondary immune response to the oral administration specific to the NEPA stronger than a response specific to NEPA caused by the NEPA in the absence of the prior immunization by injection. Applicant further claims a method where the mammal is human. Applicant further claims a method, wherein the NEPA is an antigen specific to a non-enteric pathogen selected from the group consisting of those that cause hepatitis B, hepatitis C, hepatitis delta, yellow fever, dengue hemorrhagic fever, tetanus, yaws, relapsing fever, rat bite fever,

bubonic plague and spotted fever. Applicant further claims a method wherein the human ingests sufficient plant material to provide from about 10 to about 100 micrograms of NEPA per kilogram of body weight of the human, wherein the human ingests sufficient plant material to provide from about 2 to about 5 grams of plant material per kilogram of body weight of the human, and wherein the human ingests said plant material a plurality of different times, said times being separated from each other by at least 5 days, wherein the plurality of times is three times.

Arntzen (US Patent 5,914,123) teaches methods of making a transgenic potato plant expressing an immunogen derived from hepatitis B surface antigen, wherein the immunogen is capable of eliciting an immune response in an animal by oral administration of the plant material. Arntzen also teaches methods of making a vaccine by recovering the immunogen expressed in the plant cell for use as a conventional injectable vaccine (see Claims 1-3 and 6). Moreover, Arntzen teaches that the transgenically altered plant material expressing the HBsAg can be used to both prime the mucosal immune system and/or stimulate the humoral immune response in a dose dependent manner. In Column 11, lines 36-50, Arntzen teaches that either the parenteral or non-parenteral introduction of the vaccine to a mammal can elicit serum and/or secretory antibodies against the HBsAg immunogen of the vaccine with minimal induction of systemic tolerance. Finally, Arntzen teaches that a plurality of different administrations of the genetically altered plant material expressing the HBsAg over separate periods of time provide the claimed functional effect of raising the serum IgM and IgG response specific to the hepatitis B surface antigen to achieve a secondary immune response or immunization of a mammal. Note that Arntzen specifically

teaches that the plurality of times for the administration of the vaccines in a range of 3 to 6, and that the time separating the vaccinations is in a range of 14 to 35 days to achieve protective levels of antibodies. See Column 15, lines 45-61. Arntzen (US Patent 6,136,320) teaches an anti-viral vaccine which is produced in transgenic plants, and then administered through standard vaccine introduction method or through the oral consumption of the edible portions of the plant (see ABSTRACT). The transgenic plants used in the making of the vaccines taught by Arntzen include the potato plant (see Column 16, line 43-53), and the plants are used to express various non-enteric pathogen antigens, especially hepatitis B antigen (see claims and the table found in Column 13 and 14). In Column 15, lines 3-67 to Column 16, lines 1-3, Arntzen teaches that the vaccines of his invention can be used in the making of oral vaccines, as well as, traditional injectable vaccines. Finally, Arntzen teaches the administration of multiple vaccination doses at varying intervals, as well as, periodic booster vaccinations to maintain protective levels of immunity.

Neither of the references of Arntzen expressly teach a method for providing a secondary boosting immune response in a mammal and/or a human to a non-enteric pathogen antigen (NEPA) comprising the instantly claimed method steps. However, it would have been obvious to one of ordinary skill in the art at the time the invention was made to provide the functional effect of a secondary boosting immune response in a mammal and/or a human comprising rendering the mammal immunoreceptive to a NEPA by immunization via injection of a vaccine comprising a NEPA, followed by the oral administration of a transgenic potato expressing a NEPA to cause a

secondary immune response in the immunoreceptive host, wherein the secondary immune response was stronger than the prior immunization by injection because Stites teaches the principles of immunization which can be applied to a variety of vaccine types. One of ordinary skill in the art at the time the invention was made would have been motivated to provide the claimed invention because Stites on page 724, Column 2, lines 1-42, the principles of "booster" reimmunization in a previously immune or previously primed or "immunoreceptive" individual. One of ordinary skill in the art would have been motivated to optimize either of the teachings of Arntzen by inducing a secondary boosting immune response in an individual wherein the individual ingests genetically altered potato plant material expressing the non-enteric pathogen antigen after a primary step of immunization by vaccine injection because Stites teaches that reimmunization or a "booster shot" in a previously immune or primed individual provides a rapid secondary increase in immunity. At the time the invention was made, one would have had a reasonable expectation of success that the instantly claimed method steps would have provided the functional effect of providing a secondary boosting immune response in a mammal and/or human because Stites teaches that the timing of immunization, the interval between does, and the timing of booster reimmunization are based on both theoretic considerations and vaccine trials.

Furthermore, it would have been obvious to one of ordinary skill and one would have been motivated with a reasonable expectation of success to combine the claimed method steps in a method for providing a secondary boosting immune response in a mammal and/or a human because it was well-known in the art, as readily admitted by applicant on page 3, lines 17-23 of

the present specification that, "Plants expressing hepatitis B surface antigen (HBsAg) have in fact been developed but have also disappointingly been found to create little or unacceptably low immune responses in animals ingesting them even though HBsAg isolated from plants have been found to raise an immune response when administered parenterally."

As the references indicate the various ingredients, various proportions, and various times for the administration of a vaccine, they would have been routinely optimized by one of ordinary skill in the art practicing the invention disclosed by each of the references.

According, the claimed invention was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, especially in the absence of evidence to the contrary.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michele Flood whose telephone number is (703) 308-9432. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is (703) 308-0196 or the Supervisory Patent Examiner, Michael Wityshyn whose telephone number is (703) 308-4743.

MCF

July 13, 2001

LEON B. LANKFORD, JR.
PRIMARY EXAMINER